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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,352	10/08/2003	Kyoji Ogoshi	3190-044	8311

33432 7590 07/18/2008

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400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
SIMS, JASON M	
ART UNIT	PAPER NUMBER
1631	
MAIL DATE	DELIVERY MODE
07/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,352	OGOSHI, KYOJI	
	Examiner	Art Unit	
	JASON M. SIMS	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28* is/are pending in the application.

4a) Of the above claim(s) *27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/29/2008 has been entered.

Claims 27-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventive group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/12/2007.

Claims 25-26 are the current claims hereby under examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) for the date of 4/10/2001, which has been granted.

Specification

The disclosure is objected to because of the following: Particular Figures and their descriptions are unclear as to what exactly they describe. For example, Fig. 34 is a comparison of Immunotherapy involving FL vs FF FY LL LY YY, wherein it is unclear as to what the symbols FL, FF, FY, etc. represent. It is not clear if these are particular

amino acids at the referenced position and if so, then which amino acids. If these are not amino acids, it is unclear as to what exactly is being compared in the instant Fig. The specification appears to be silent as to what exactly the instant symbols refer along with the same deficiency applied to other Fig. descriptions as well.

Appropriate correction is required.

The following is a rejection being newly made:

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for correlating genetic polymorphisms of three specific genes with stomach cancer treatment, does not reasonably provide enablement for correlating genetic polymorphisms of the three specific genes with Any cancer.

Breath of Claims

The breath of the claims is overly broad is they are drawn to a method of determining treatments for a cancer patient having **any** type of cancer based on the amino acids encoded at particular positions in three HLA class genes.

Specification

The specification provides correlations of these particular alleles and encoded amino acids, specifically to stomach cancer, and cancer treatments. However, the specification does not provide guidance as to how to apply the knowledge of these alleles and encoded amino acids to **all** other types of cancer. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to apply knowledge of the invention commensurate in scope with these claims. Furthermore, Figs 4, 5, and 6 seem to disclose similar accumulated survival rates using immunotherapy, chemotherapy, and cancer resection alone based on the same alleles of the DQB1* 050301 gene. Therefore, it is unclear from the specification as to how the specific alleles and encoded amino acids determine treatment for cancer patients.

Prior Art

The prior art, i.e. Bateman et al. (1999), in the summary indicates HLA class II genes and specifically the three claimed in the instant application, may be related to cancer but do not teach the relevance of these particular alleles with determining cancer treatments in **all** cancers.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Claim Rejections - 35 USC § 112-Second Paragraph

Response to Arguments:

Applicant's arguments, filed 12/31/2008, with respect to the rejections under 35 USC 112 second paragraph have been fully considered and are persuasive because of applicant's amendments to the claims and arguments. Therefore the rejections are have been withdrawn.

The followings rejections are being newly made:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recites the wording "determining what amino acids are encoded by one or more of positions..." "of the" and then recites the three different genes in each of the three different method steps. Specifically the wording "one or more of positions" with respect to wording "of the HLA DQB1* gene", is vague and indefinite. It is unclear if the wording "one or more positions" refers to the position along the nucleotide sequence comprising the gene or the amino acid sequence comprising the protein, such as that of the translation of the HLA DQB1 gene. The wording "one or more positions" is also unclear because it appears to refer to the positions along the nucleotide sequence wherein the wording "one or more positions" does not appear to be defined as

comprising three nucleotides. Therefore, if the wording "one or more positions" refers to places along the nucleotide sequence, it is unclear as to how one position, i.e. one nucleotide, may determine an amino acid sequence. However, it further appears that the word may read on the amino acid sequence as in Example 8 from the specification, the applicant states " In stomach cancer cases, I on DP65 (Position 65 on the amino acid sequence)," which indicates that the word positions refers to the amino acid sequence. Clarification via clearer claim wording is required.

Claim 25 recites a method for determining a cancer treatment based on the amino acids encoded at particular positions of three different particular class II HLS genes. It is unclear as to how determined amino acids encoded at particular positions of the three distinct genes effects the determination of a cancer treatment. For instance, it is unclear as to how different will the determination of a cancer treatment be based on how different the amino acids are encoded at the particular positions. Furthermore, it appears vague and indefinite as to how different the determination of a cancer treatment will be based on the all the different possible combinations of encoded amino acids at all the different combinations of positions in each of the three distinct genes. Clarification via clearer claim wording is required.

Claim Rejections - 35 USC § 103

Response to Arguments:

Applicant's arguments with respect to the rejection of claims 25 and 26 have been considered but are moot in view of the new ground(s) of rejection.

The following rejection is being newly made:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al. (J. Clinical Oncology, vol. 19, pp. 1279-1287, 2001) in view of Bateman et al. (1999) and further in view of Lee et al. (Gastroenterology, vol. 111, pp. 426-432, 1996) and further in view of Santamaria et al. (US P/N 5,972,604) as evidenced by F.Lv et al. (2004) and NCBI.

The claims are directed to a method for determining treatments for a cancer patient comprising determining what amino acids are encoded by one or more of a number of positions of the HLA DQB1 *gene, determining what amino acids are

encoded by one or more of a number of positions of the DRB1 *gene, determining what amino acids are encoded by one or more of a number of positions of the DPBI *gene, and correlating the amino acids encoded at the positions with a cancer treatment having the greatest statistically significant probability of prolonging the cancer patient's survival, wherein the cancer treatment comprises immunotherapy, chemotherapy, resection, or a combination thereof.

Davies et al. teach a method for evaluating cancer treatments based on genotyping polymorphic genes of patients receiving cancer therapy and correlating the survival results of patients containing a specific polymorphic gene with appropriate cancer treatment regimens (see abstract, p. 1279). The reference teaches that the polypeptide encoded by polymorphic genes of Glutathione S-transferase, i.e., namely theta (GSTT1) and mu (GSTM1), affect the cytotoxicity of chemotherapeutic drugs. Experimental DNA typing data of Glutathione S-transferase polymorphic genes were obtained from a patient population of children with acute myeloid leukemia or AML (see Table 1 and GST Genotyping, p. 1280) receiving chemotherapy (see Chemotherapy Treatment Regimen). GSTT1 and GSTM1 genotype outcome differences in overall survival, disease-free survival and relapse-free survival were statistically analyzed (see Statistical Analysis, p 1280, Figures 1-5, pp.1281-1282, and Tables 2-3, pp. 1282-1283) and further lead to the conclusion that children lacking GSTT1 had greater toxicity and reduced survival rate after chemotherapy for AML compared with children with at least one GSTT1 allele, wherein the genotype might be of useful in selecting appropriate chemotherapy regimens for children with AML (see last paragraph of p. 1284).

Davies et al. does not teach any association of HLA class II genes with any cancer.

Bateman et al. in the summary, page 234, right column, first paragraph, discuss HLA genes and an association with cancer. Bateman et al. discuss different alleles having different associations with cancer as well. Furthermore, Bateman et al. at page 233, discuss specifically the DQB1, DRB1, and DPB1 genes and alleles and their associations with particular cancers. Bateman et al. at page 234 second column, last paragraph and page 235, left column, first paragraph state that HLA genotypes may help to predict treatment success in cancer patients and gives an example of specific HLA-DRB1 alleles and the response to particular therapy in a particular cancer.

Bateman et al. does not specifically teach correlations between the specific HLA class II genes and stomach cancer or treatment.

However, the references of Lee et al. (see line 1-2, col. 1, p. 426) and Santamaria et al. (col. 3, lines 1-67, col. 4, lines 1-7, col. 9, lines 60-68, and col. 10, lines 1-16) teach HLA Class II genes are associated with several cancers, including the DRB1, DQB1, and the DPB1 genes. Namely, "HLA-DQB1*0310 is more common in Caucasian patients with gastric adenocarcinoma than noncancer controls" (Lee et al. see conclusions, p. 426).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the instant invention to use the genotyping methods of Davies et al. or Lee et al. or Santamaria et al. along with the statistical methods of Davies et al. to identify HLA Class II polymorphic genes of patients receiving cancer therapy and correlating the

survival results of HLA Class II genotype with appropriate cancer treatment regimens as suggested by Bateman et al. It is well known in the art to have some success with tailoring a treatment to a genomic profile as taught by Davies. Furthermore, it is well known in the art that there is an association or correlation between HLA class II genes, specifically DRB1, DQB1, and DPB1, their alleles and cancers, including stomach as taught by Lee et al. and Santamaria et al. Moreover, it has even been specifically suggested to determine cancer treatments based on HLA class II alleles as taught by Bateman et al. Therefore, one of ordinary skill in the art would have been obvious to have used specifically encoded amino acids at particular positions in the DRB1, DQB1, and DPB1 HLA class II genes to determine a cancer treatment with a reasonable expectation of success as taught by Bateman et al. Because of the extensive cancer polymorphic genotyping of Lee et al. and Santamaria et al. and the productive results of cancer polymorphic genotyping of Davies et al., one would have been motivated by Bateman et al. who states that "HLA genotypes may help to predict treatment success in cancer patients" to combine the references.

Furthermore, Bateman et al., as stated above, teaches several different alleles of said genes and their associations with cancer, but does not specifically reference amino acid positions of particular genes, such as position 6 of the DPB1 gene. However, after a cursory glance at a comparison between the amino acid sequence of the DPB1 gene as stored in the NCBI database and the amino acid sequence in the DPB1*0501 allele, as taught by Bateman et al., it is obvious that there are variations in the amino acid positions, such as position 6 as outlined below in bold.

DPB1 gene: A human DPB1 gene, referenced from the NCBI website specifically at (http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=X97406.1):

agaattacgt gtaccagtta cggcaggaat gctacgcgtt taatgggaca cagcgcttcc tggagagata catctacaac cgggaggagt tcgtgcgctt cgacagcgac gtgggggagt tccgggcggt gacggagctg gggcggcctg atgaggacta ctggaacagc cagaaggacc tcctggagga gaggcgggca gtgccggaca ggatgtgcag acacaactac gagctggacg aggccgtgac c

The sequence was then pasted into the translate tool at www.expasy.org specifically at http://ca.expasy.org/tools/dna.html to obtain the following Amino Acid sequence, wherein Frame 1 was selected:

R I T C T S Y G R N A T R L M G H S A S W R D T S T T G R S S C A S T A T W G S S G R **Stop** R S W G G L M R T T G T A R R T S W R R G G Q C R T G C A D T T T S W T R P **Stop**

DPB1*0501 allele: An allele from a referenced from F. Lv et al., at page 513

```
1 10 20 30 40 50
DPB1*0102 AGAATTACCTTTTCCAGGGACGGCAGGAATGCTACGCGTTTAATGGGACA
DPB1*0202 --------------------------------------------------
DPB1*2401 --------------------------------------------------
DPB1*0501 --------------------------------------------------
60 70 80 90 100
DPB1*0102 CAGCGCTTCCTGGAGAGATACATCTACAACCGGGAGGAGCTCGTGCGCTT
DPB1*0202 ----------------------------------------------------
DPB1*2401 ----------------------------------------T---C------
DPB1*0501 ----------------------------------------------------
110 120 130 140 150
DPB1*0102 CGACAGCGACGTGGGGGAGTTCCGGGCGGTGACGGAGCTGGGGCGGCCTG
DPB1*0202 ----------------------------------------------------
DPB1*2401 ----------------------------------------------------
DPB1*0501 ----------------------------------------------------
160 170 180 1 9 0 200
DPB1*0102 AGGCGGAGTACTGGAACAGCCAGAAGGACATCCTGGAGGAGAAGCGGGCA
DPB1*0202 ----------------------------------------G---------
DPB1*2401 ----------------------------------------------------
DPB1*0501 ----------------------------------------------------
210 220 230 240 250
DPB1*0102 GTGCCGGACAGGATGTGCAGACACAACTACGAGCTGGGCGGGCCCATGAC
DPB1*0202 ----------------------------------------------------
DPB1*2401 ----------------------------------------------------
DPB1*0501 ----------------------------------A--A-C--G------
260
DPB1*0102 CCTGCAGCGCCGAG
DPB1*0202 --------------
DPB1*2401 --------------
DPB1*0501 --------------
```

The gene was pasted together with the proper nucleotide substitutions as indicated in the

reference:

AGAATTACCT TTTCCAGGGA CGGCAGGAAT GCTACGCGTT TAATGGGACA
CAGCGCTTCC TGGAGAGATA CATCTACAAC CGGGAGGAGC TCGTGCGCTT
CGACAGCGAC GTGGGGGAGT TCCGGGCGGT GACGGAGCTG GGGCGGCCTG
AGGCGGAGTA CTGGAACAGC CAGAAGGACA TCCTGGAGGA
GAAGCGGGCA GTGCCGGACA GGATGTGCAG ACACAACTAC GAGCTGGACG
AGCCCGTGAC CCTGCAGCGC CGAG

The sequence was then pasted into the translate tool at www.expasy.org specifically at http://ca.expasy.org/tools/dna.html to obtain the following Amino Acid sequence, wherein Frame 1 was selected:

R I T F S R D G R N A T R L M G H S A S W R D T S T T G R S S C A S T A T W G S S G R **Stop** R S W G G L R R S T G T A R R T S W R R S G Q C R T G C A D T T T S W T S P **Stop** P C S A E

Comparison

DPB1 Human gene translated amino acid sequence:

R I T C T S Y G R N A T R L M G H S A S W R D T S T T G R S S C A S T A T W G S S G R **Stop** R S W G G L M R T T G T A R R T S W R R G G Q C R T G C A D T T T S W T R P **Stop**

DPB1*0501 Human gene allele translated amino acid sequence:

R I T F S R D G R N A T R L M G H S A S W R D T S T T G R S S C A S T A T W G S S G R **Stop** R S W G G L R R S T G T A R R T S W R R S G Q C R T G C A D T T T S W T S P **Stop** P C S A E

Therefore, because of the obvious variations in the amino acids at particular positions between the standard gene and its alleles, one of ordinary skill in the art would be further motivated to search for correlations between genotypes and treatments for cancer as stated by Bateman et al. at page 234 second column, last paragraph and page 235, left column, first paragraph, whom states "that HLA genotypes may help to predict treatment success in cancer patients." One of ordinary skill in the art at the time of the instant invention would then also be motivated to look at correlations between genotypes, i.e. the amino acids at specific positions, such as those cited in the instant claims, and treatments in all three referenced genes.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason Sims, whose telephone number is (571)-272-7540.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Marjorie Moran can be reached via telephone (571)-272-0720.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

// Jason Sims //

/Michael Borin, Ph.D./

Primary Examiner, Art Unit 1631